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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,607	11/08/2001	Richard T. Lee	B0801.70231US00	6830

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Elizabeth Robin Plumer
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Ave.
Boston, MA 02210

EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,607	LEE, RICHARD T.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,10 and 37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,10 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/2/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/2/2006 has been entered.

2. Claims 1, 6-8, 10, and 37-48 are currently pending and are the subject of this office action.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 10/7/2005.

Information Disclosure Statement

The information disclosure statement received on 6/2/2006 has been fully considered by the Examiner.

Claim Objections

Objection to claim 8 regarding the term "the polypeptide" in parts (*iii*) and (*iv*), as set forth on p. 2 of the office action mailed on 3/29/2006, is *withdrawn* in response to Applicant's amendment to part (*iii*) to recite "the polypeptide of part (*ii*)", and Applicant's cancellation of part (*iv*).

Claim Rejections - 35 USC § 112, first paragraph - enablement

Rejections withdrawn

1. Rejection of claims 8, 10, and 42-48 under 35 USC § 112, first paragraph, regarding lack of enablement for methods of diagnosing a cardiovascular disease by monitoring a sample from a patient for an antibody which selectively binds a polypeptide or peptide, as set forth on p. 3-4 of the office action mailed on 3/29/2006, is *withdrawn* in response to Applicant's cancellation of claim 8, part (*iv*) and claim 10, part (c).

2. Rejection of claims 1, 6-8, 10, and 37-48 under 35 USC § 112, first paragraph, regarding lack of enablement for methods of diagnosing a cardiovascular disease by detecting Fit-1 in a biological sample, as set forth on p. 5-6 of the office action mailed on 3/29/2006, is *withdrawn* in response to the Applicant's arguments that the specification is enabling for detection of proteins in samples other than blood or serum, such as urine, because the specification, when combined with what is known in the art, would allow a skilled artisan to practice the claimed invention. Specifically, the Applicant notes that detection of proteins in samples other than blood or serum, such as urine, is well-known in the art. Furthermore, the Applicant argues that detection of N-terminal pro-brain natriuretic peptide in urine is diagnostic for cardiovascular disease, and therefore one of ordinary skill in the art would be familiar with detection of proteins in urine. Finally, the Applicant argues that Fit-1/ST2 expression is increased in various tissues after cardiovascular disease, including left ventricular tissue, and lung, thymus, spleen, atrium, and liver tissues. In view of the specification, which contemplates determination of Fit-1 levels in tissues other than serum or blood, this argument has been found persuasive, and accordingly, the rejection is withdrawn.

3. Rejection of claims 10, 39, and 45-46 under 35 USC § 112, first paragraph, regarding lack of enablement for contacting a sample with a detectable agent, such as "(a) an isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of (i)", as set forth on p. 6 of the office action mailed on 3/29/2006, is *withdrawn*. In the response received on 6/2/2006, the Applicant argues that the specification teaches that aberrant expression of Fit-1 is diagnostic for cardiovascular disease. The Applicant further argues that a person of ordinary skill in the art would be familiar with hybridization methodology, and because the sequence of many Fit-1

molecules is known, the design of primers and/or probes specific for detecting Fit-1 would be routine. Furthermore, the Applicant notes that the specification provides guidance for detection of Fit-1 using non-full-length Fit-1 nucleic acids. Taken together, the Applicant asserts that the specification is enabling for detection of Fit-1 by contacting a sample with a detectable agent, such as "(a) an isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of (i)". These arguments have been fully considered and are found persuasive. Accordingly, the rejection is withdrawn.

Rejections maintained and/or necessitated by amendment

4. Claims 1, 6-8, 10, and 37-48 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for "aberrant" expression of Fit-1 being diagnostic of cardiovascular disease, and determination of the stage of cardiovascular disease by determining Fit-1 levels, as set forth on p. 4-5 of the office action mailed on 3/29/2006. In the response received on 6/2/2006, the Applicant amended the claims to cancel the term "aberrant", and instead read on a method of diagnosing cardiovascular disease based on increased Fit-1 levels, wherein expression of Fit-1 that is "increased relative to a predetermined value" is diagnostic of cardiovascular disease. Additionally, the Applicant has amended the claims to read on a method of determining "regression, progression or onset" of a cardiovascular condition, instead of determining the stage of a cardiovascular condition. The Applicant argues that the specification is enabling for monitoring Fit-1 expression for determining regression, progression, or onset of cardiovascular disease, as evidenced by p. 68, which describes differences in Fit-1 expression over time as the cardiovascular conditions changes with time.

These arguments have been fully considered and are not found persuasive. Regarding methods for diagnosis of cardiovascular disease by Fit-1 levels that are "increased relative to a predetermined value", the breadth of the claims is broad because the claims could read on diagnosis of cardiovascular disease based on any Fit-1 level higher than zero, wherein said level may be diagnostic of cardiovascular disease, or may merely represent normal, baseline levels of Fit-1 expression. Furthermore, the specification does not disclose a predetermined value of Fit-1 expression, or provide guidance or examples showing how to determine or calculate a predetermined value of Fit-1 expression in healthy patients with which to compare test results. The specification on p. 68 and the drawings submitted with the application show a transient increase in Fit-1 expression that then decreases over time, but the specification does

not disclose what levels are present in healthy tissues. Figures 1 and 3 show detectable Fit-1 expression in non-stretched cells, suggesting that Fit-1 is detectable, albeit at low levels, in normal, healthy tissue. Thus, it is not apparent that the low Fit-1 levels reported 14 and 90 days after a heart attack (see p. 68) would be higher than any predetermined value based on the Fit-1 expression levels of non-stretched (i.e. healthy) cells. Because Fit-1 apparently can be detected in normal, healthy cells, a person of ordinary skill in the art would not be able to predict a value for comparison to test samples, and would require undue experimentation to determine such a value.

Similarly, the teachings and examples in the specification do not teach one of ordinary skill in the art how to assess regression, progression, or onset of a cardiovascular disease by determining Fit-1 levels. The specification teaches that Fit-1 levels increase in response to a cardiovascular disease-associated event such as a heart attack, and then decline over time. However, the specification does not adequately teach how to equate levels of Fit-1 expression with regression, progression, or onset of a cardiovascular disease. For example, if a peak Fit-1 expression level of 5 is diagnostic of cardiovascular disease, then a value of 2.5 could represent either progression or regression. However, without multiple measurements over time, one would not know if the measured Fit-1 value of 2.5 represents levels of Fit-1 that are increasing, and thus presumably indicative of disease progression, or if the value of 2.5 represents levels of Fit-1 that are decreasing, thus representing disease regression. Because of the unpredictability resulting from a single Fit-1 measurement, a person of ordinary skill would not be able to correlate Fit-1 levels with disease progression, regression, or onset, regardless of whether the Fit-1 values exceed a predetermined value.

In summary, due to the excessive breadth of the claims, which read on a method of diagnosing cardiovascular disease by comparing Fit-1 levels to a predetermined value, wherein said value could be any value greater than zero, the lack of guidance and examples in the specification showing how to determine such a value to which test results should be compared, and the unpredictability inherent in the art and the instant invention regarding how to determine such a level, a person of ordinary skill in the art would require further, undue experimentation to calculate a "predetermined value" of Fit-1 expression that would be diagnostic of cardiovascular disease when said value is exceeded. In addition, due to the lack of guidance and example in the specification showing how to determine regression, progression, or onset of cardiovascular disease based on any Fit-1 expression level that is greater than a predetermined value, and the

unpredictability inherent in the art and the instant invention regarding how to correlate a specific Fit-1 expression level with a specific disease stage, one of ordinary skill in the art would require further, undue experimentation to determine regression, progression, or onset of all cardiovascular diseases based on a single determined Fit-1 level, wherein said level is greater than a predetermined value.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejection of claims 10, 39, and 44-45 under 35 USC § 112, first paragraph, regarding lack of written description for methods of diagnosis of cardiovascular conditions by determining expression of Fit-1 nucleic acids and polypeptides, as set forth on p. 7 of the office action mailed on 3/29/2006, is *withdrawn*. In the response received on 6/2/2006, the Applicant argues that the instant application is drawn to methods of diagnosing cardiovascular disease, and not Fit-1 sequences *per se*, and that Fit-1 nucleic acid sequences were well-known in the art at the time the instant invention was conceived. The Applicant further argues that the specification provides guidance and examples in which nucleic acids of various sizes and compositions are used, and thus the specification had adequately described the genus of Fit-1 nucleic acids and polypeptides that are capable of hybridizing to Fit-1, and whose hybridization to Fit-1 is diagnostic of cardiovascular disease. These arguments have been fully considered and are found persuasive. Accordingly, the rejection under 35 U.S.C. 112, first paragraph, is withdrawn.

Claim Rejections - 35 USC § 112, second paragraph

Rejections withdrawn

Rejection of claims 1, 6-7, and 37-41 under 35 USC § 112, second paragraph, as being incomplete for omitting essential method steps, as set forth on p. 8 of the office action mailed on 3/29/2006, is *withdrawn* in response to the Applicant's amendments to the claims to read on a method of diagnosing cardiovascular disease characterized by increased Fit-1 expression, wherein increased Fit-1 expression relative to a predetermined value is diagnostic of cardiovascular disease. In the response received on 6/2/2006, the Applicant argues that the method of the instant invention does not require additional Fit-1 determinations because of the

amendments to the claims to read on comparison of measured Fit-1 levels to a predetermined value, wherein expression that is increased relative to this predetermined value is indicative of cardiovascular disease. This argument has been fully considered and is found persuasive. Accordingly, the rejection under 35 U.S.C. 112, second paragraph, is withdrawn.

Rejections maintained and/or necessitated by amendment

Claims 8, 10, and 42-48 *remain rejected* under 35 USC § 112, second paragraph, for being incomplete for omitting essential method steps, as set forth on p. 8 of the office action mailed on 3/29/2006. In the response received on 6/2/2006, the Applicant argues that the method of the instant invention does not require determination of Fit-1 expression at two more or time points, because as currently amended, the claims read on determination of Fit-1 expression wherein expression that is increased relative to a predetermined value is indicative of cardiovascular disease, and because the method merely requires comparison relative to a predetermined value, no additional Fit-1 measurements are necessary.

This argument has been fully considered and not found persuasive. While the Examiner agrees that one of ordinary skill in the art could diagnose cardiovascular disease based on a single determination of Fit-1 expression, wherein the assessed Fit-1 level is increased relative to a predetermined value, and wherein that predetermined value reflects Fit-1 expression in a healthy individual, the claims as currently amended also read on determining regression, progression, or onset of cardiovascular disease by determining Fit-1 expression. As stated above in the 35 U.S.C. 112, first paragraph enablement rejection, a person of ordinary skill in the art would not be able to correlate any observed Fit-1 expression level with progression, regression, or onset of any cardiovascular disease, without multiple measurements to determine whether Fit-1 levels are increasing (and presumably indicative of disease onset and/or progression), or decreasing (presumably indicative of disease regression).

Double Patenting

Rejection withdrawn

Rejection of claims 1, 6-8, 10, and 37-48 under the judicially-created doctrine of obviousness-type double patenting over claims 1-3 and 7-11 of co-pending application

10/435,482, is withdrawn in response to the Applicant's cancellation of claims 1-3 and 7-11 of co-pending application 10/435,482 on 5/22/2006.

Rejection maintained and/or necessitated by amendment

Claims 1, 6-8, 10, and 37-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-37, 46-47, 51-55, and 64-66 of copending Application No. 10/435,482. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications are drawn to diagnostic methods for cardiovascular disease comprising determining Fit-1 levels. Co-pending application 10/435,482 is drawn to correlating expression of IL-1RL-1, which the specification defines as being synonymous with Fit-1 (p. 2, line 24), with the outcome of cardiovascular disease, while the claims of the instant application are drawn to diagnosing cardiovascular disease by determination of Fit-1 levels. The instant application is also drawn to predicting progression, regression, or onset of cardiovascular disease, and both applications are drawn to methods based on comparing Fit-1/IL1RL-1 levels to a predetermined value. Furthermore, both applications are drawn to methods of determining Fit-1/IL1RL-1 in a biological sample, including serum or blood, and both applications recite cardiac hypertrophy, myocardial infarction, stroke, arteriosclerosis, and heart failure as diseases that can be diagnosed, or for which the outcome can be predicted, by measuring Fit-1/IL1RL-1 levels.

Therefore, it would be obvious to one of ordinary skill in the art that the methods of the instant application and co-pending application 10/435,482 are not patentably distinct. Both applications claim methods of assessing Fit-1/IL1RL-1 levels, and because the instant application claims a method for predicting progression, regression, or onset of cardiovascular disease by measuring Fit-1 expression, both applications are drawn to methods of predicting an outcome of cardiovascular disease. Furthermore, because the method steps, samples, and recited cardiovascular diseases are essentially the same, the skilled artisan would recognize that the methods of the instant application could be encompassed by the claims of co-pending application 10/435,482, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER